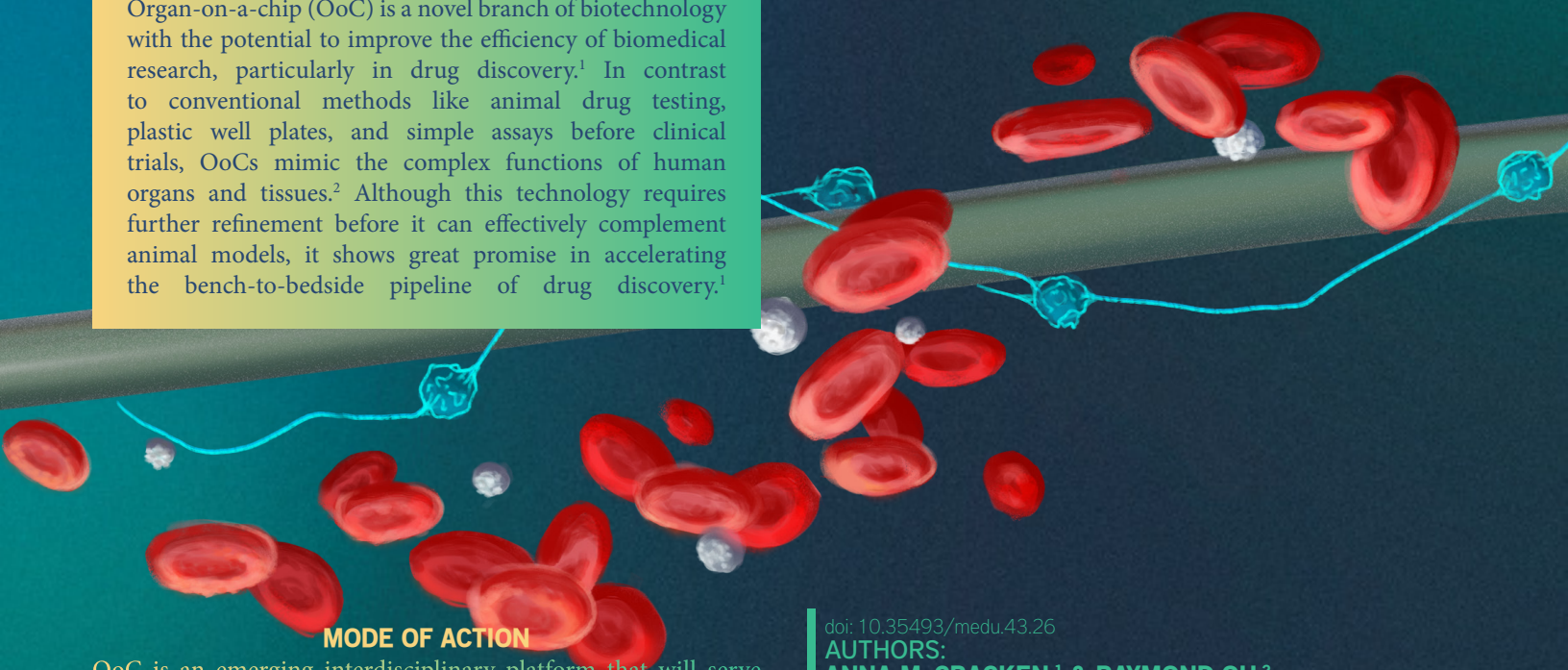
ORGAN-ON-A-CHIP

BIOTECH BLUEPRINT

INTRODUCTION

Organ-on-a-chip (OoC) is a novel branch of biotechnology with the potential to improve the efficiency of biomedical research, particularly in drug discovery.[1] In contrast to conventional methods like animal drug testing, plastic well plates, and simple assays before clinical trials, OoCs mimic the complex functions of human organs and tissues.[2] Although this technology requires further refinement before it can effectively complement animal models, it shows great promise in accelerating the bench-to-bedside pipeline of drug discovery.[1]



MODE OF ACTION

OoC is an emerging interdisciplinary platform that will serve as an important tool in tissue analysis and drug screening.[3,4] OoCs combine human-derived cells with microfluidic networks of perfused chambers that recreate physicochemical microenvironments to mimic the microarchitecture and function of specific tissues or organs.[4-6] Physiological functions and mechanical stimuli of organs can be recreated and manipulated by altering various characteristics of OoCs, including their 3D microarchitecture or fluidic channels.[6] Many design variations in 3D microarchitecture exist depending on which specific tissue interaction the OoC is designed to recreate.[4] For example, multi-layered microfluidic devices are compartmentalized by porous membranes that can recreate natural barrier structures, such as the blood-brain or intestinal mucosal barrier.[4,7,8] Variables such as barrier integrity can then be measured with transendothelial/epithelial electrical resistance to assess material transport between tissues in drug screening.[4,7] Furthermore, the various gradients in biological organs are replicated by the flowing culture medium in microchannels via engineered pumps.[9] These channels enable long-term culture of cells in the chip through the refreshment of a flowing culture medium, while also replicating the fluid shear stress that cells may experience in the body.[4,9] Mechanical functions of organs, such as the breathing motion in the lungs or the peristaltic motion in the gut, may also be mimicked through the use of a micro-diaphragm or side vacuum channels to stretch porous membranes.[4] Although OoC is a relatively new field of study, researchers have made rapid progress in terms of developing more specific mechanisms to model various types of organs and tissue samples in a chip microenvironment.[6]

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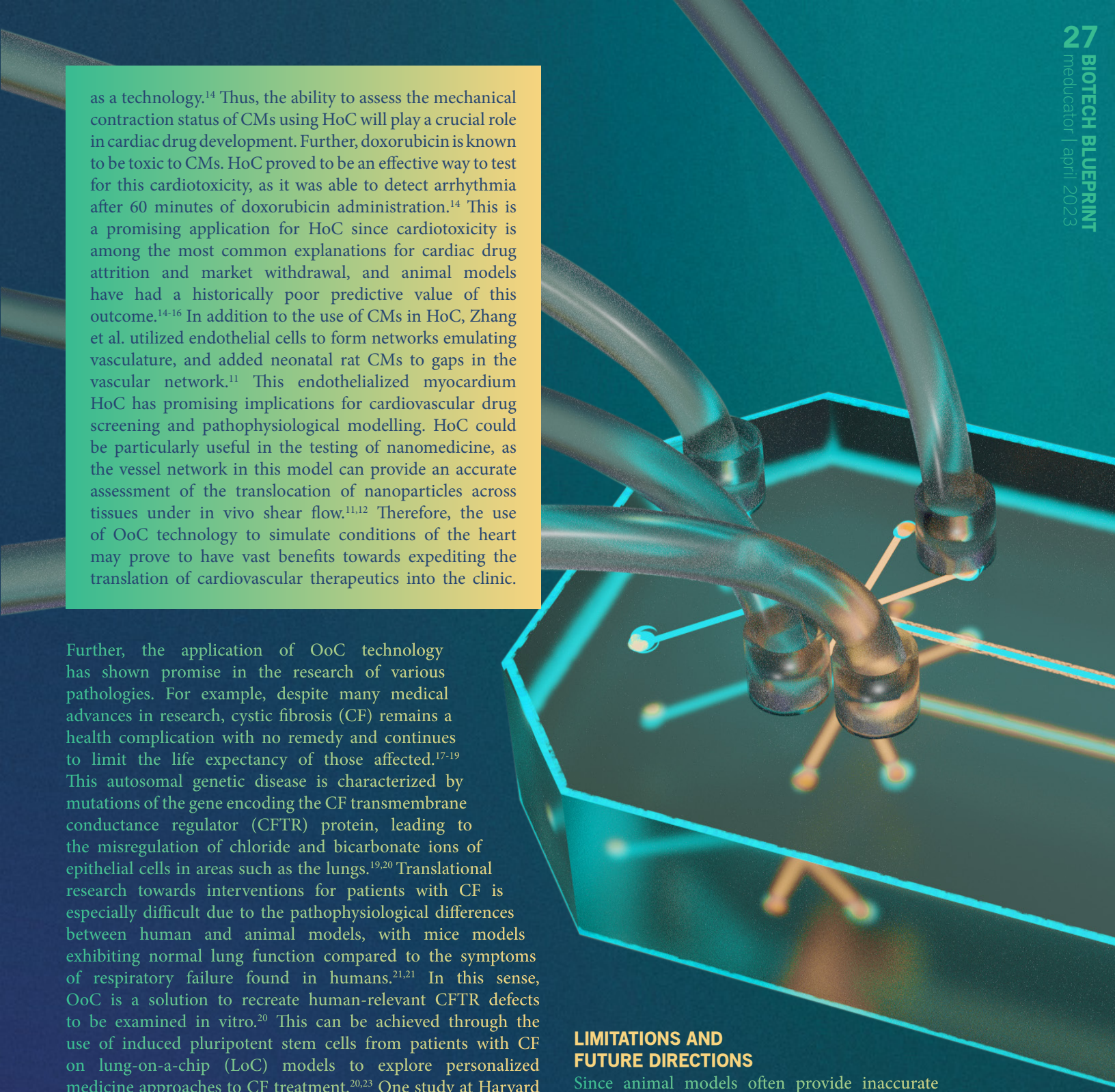
APPLICATIONS

OoC has been employed to simulate the cellular microenvironment of many organs and tissues of the human body, including the heart.[1] Emerging research has used cardiomyocytes (CMs) implanted in a polydimethylsiloxane (PDMS) model to create a heart-on-a-chip (HoC), used to evaluate the efficacy of cardiac drugs and their toxicity to CMs.[10,11,13,14] In a study conducted in 2016, HoC was used to measure CM response to both verapamil—a calcium channel blocker—and doxorubicin—an anticancer drug with known adverse effects on the heart, including arrhythmia and cardiomyopathy.[14] In HoC, individual CMs aggregate and form a functional syncytium to perform tissue-level contraction—the status of this contraction upon drug administration was assessed by rate, magnitude, and pattern.[14] This technology provides more information compared to the typical electrophysiological recording of individual CMs, which does not tell us how these cells work together as a tissue and are, therefore, less predictive

as a technology.[14] Thus, the ability to assess the mechanical contraction status of CMs using HoC will play a crucial role in cardiac drug development. Further, doxorubicin is known to be toxic to CMs. HoC proved to be an effective way to test for this cardiotoxicity, as it was able to detect arrhythmia after 60 minutes of doxorubicin administration.[14] This is a promising application for HoC since cardiotoxicity is among the most common explanations for cardiac drug attrition and market withdrawal, and animal models have had a historically poor predictive value of this outcome.[14-16] In addition to the use of CMs in HoC, Zhang et al. utilized endothelial cells to form networks emulating vasculature, and added neonatal rat CMs to gaps in the vascular network.[11] This endothelialized myocardium HoC has promising implications for cardiovascular drug screening and pathophysiological modelling. HoC could be particularly useful in the testing of nanomedicine, as the vessel network in this model can provide an accurate assessment of the translocation of nanoparticles across tissues under in vivo shear flow.[11,12] Therefore, the use of OoC technology to simulate conditions of the heart may prove to have vast benefits towards expediting the translation of cardiovascular therapeutics into the clinic.

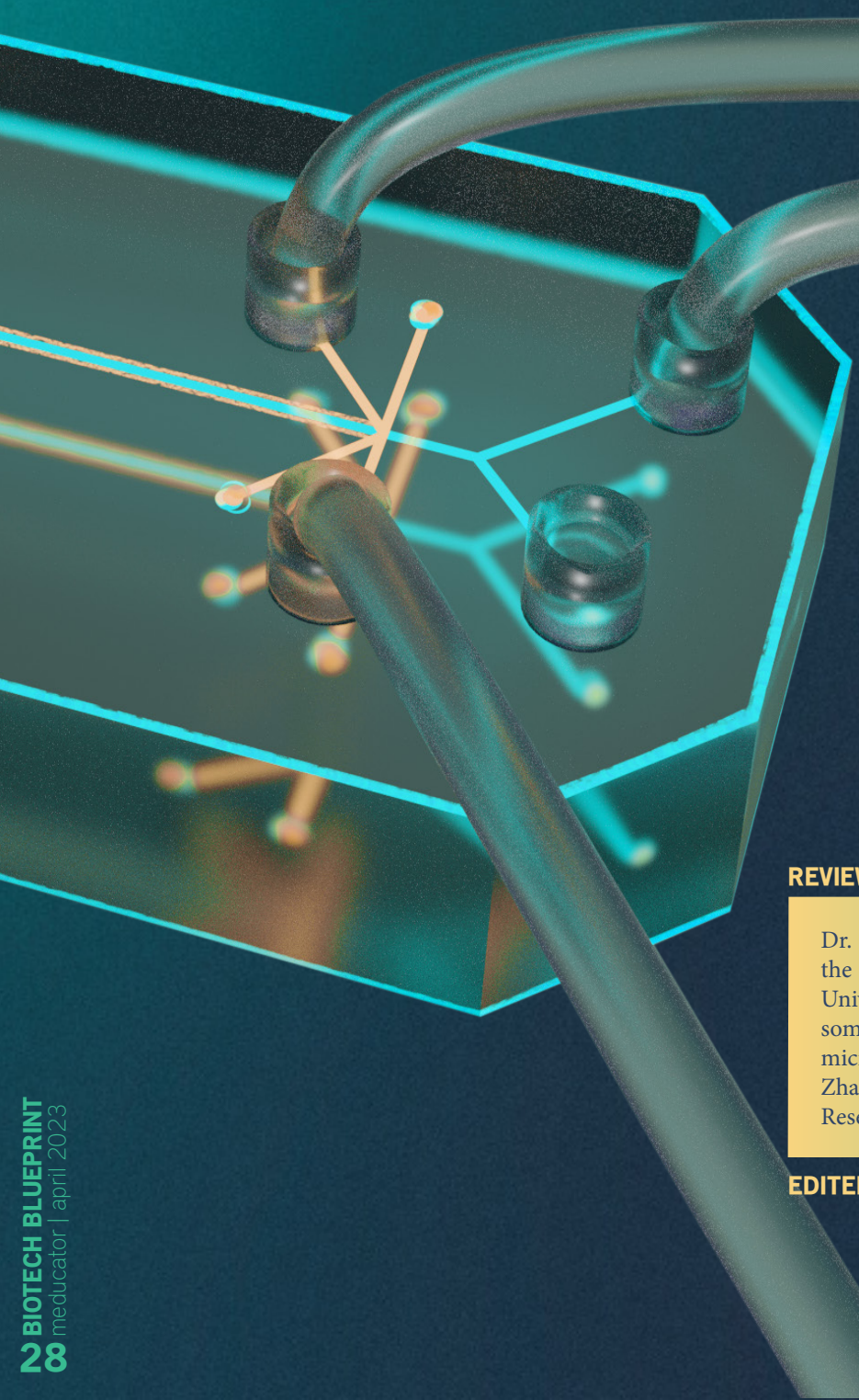


Further, the application of OoC technology has shown promise in the research of various pathologies. For example, despite many medical advances in research, cystic fibrosis (CF) remains a health complication with no remedy and continues to limit the life expectancy of those affected.[17-19] This autosomal genetic disease is characterized by mutations of the gene encoding the CF transmembrane conductance regulator (CFTR) protein, leading to the misregulation of chloride and bicarbonate ions of epithelial cells in areas such as the lungs.[19,20] Translational research towards interventions for patients with CF is especially difficult due to the pathophysiological differences between human and animal models, with mice models exhibiting normal lung function compared to the symptoms of respiratory failure found in humans.[21,21] In this sense, OoC is a solution to recreate human-relevant CFTR defects to be examined in vitro.[20] This can be achieved through the use of induced pluripotent stem cells from patients with CF on lung-on-a-chip (LoC) models to explore personalized medicine approaches to CF treatment.[20,23] One study at Harvard University showed that OoC models lined with CF patient cells recapitulate many features of CF symptoms including impaired airway mucociliary clearance, inflammation, and respiratory insufficiency.[23] This study highlighted that genetic diseases could be modelled via OoCs using different cell linings, and that their accuracy was closely related to the clinical symptomatology of CF.[23] CF LoCs featured higher levels of pro-inflammatory cytokines and a favourable bacteria growth environment as compared to normal LoCs.[23,24] As the research behind OoC progresses, their ability to mimic various human diseases and compare their mechanisms to healthy organ chips in vitro will prove to be vital for the translational medicine of many specific diseases.[6,23]

LIMITATIONS AND FUTURE DIRECTIONS

Since animal models often provide inaccurate information regarding the efficacy and toxicity of drugs in humans, OoC provides an opportunity to remedy this research gap and vastly reduce the unnecessary costs of pre-clinical trials due to both drug attrition and animal models.[16,25] While some key applications of OoC have been outlined in this review, many speculate that the future of this technology could extend across many interdisciplinary fields in medicine.[2] Although some experts postulate the possibility of a human-on-a-chip, this is not the goal of OoC. Rather, the goal is to better understand inter-organ interactions and address the specific research questions at hand. However, there are still major developments that must occur to achieve this goal.[1] For example, while PDMS has proven to be a valuable material

for OoC, it has several limitations, including a decreased absorbance of small hydrophobic molecules.[1] Furthermore, the small dimensions of this technology results in a larger surface area to volume ratio, thus misrepresenting the accurate amount of a drug being absorbed as compared to in vivo studies.[26] Further research into alternative materials is necessary to construct more complex OoC models.[2,27] For novel drugs, OoC allows for human-relevant drug experimentation even before clinical trials and may aid researchers in predicting drug response variations before the clinical stage. Moreover, when targeting rare disorders where obtaining sufficient participant numbers is difficult, OoC could provide a forum for pre-clinical trials using cells from patients all around the world.[2] Thus, OoC has the potential to revolutionize the process of pre-clinical drug discovery.



1. Wu Q, Liu J, Wang X, Feng L, Wu J, Zhu X, et al. Organ-on-a-chip: Recent breakthroughs and future prospects. Biomed Eng OnLine. 2020;19(1):9. Available from: doi:10.1186/s12938-020-0752-0.
2. Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet. 2022;23(8):467–9. Available from: doi:10.1038/s41576-022-00466-9.
3. Ahadian S, Civitarese R, Bannerman D, Mohammadi MH, Lu R, Wang E, et al. Organ-on-a-chip platforms: A convergence of advanced materials, cells, and microscale technologies. Adv Healthc Mater. 2018;7(2):1700506. Available from: doi:10.1002/adhm.201700506.
4. Cho S, Lee S, Ahn SI. Design and engineering of organ-on-a-chip. Biomed Eng Lett. 2023;1-13. Available from: doi:10.1007/s13534-022-00258-4.
5. Park J, Kim KB, Lee J, Kim HC, Huh D. Organomimetic microsystems technologies. Biomed Eng Lett. 2012;2(2):88–94. Available from: doi:10.1007/s13534-012-0059-6.
6. Maschmeyer I, Kakava S. Organ-on-a-chip. Adv Biochem Eng Biotechnol. 2022;179:311-42. Available from: doi:10.1007/10_2020_135.
7. Ahn SI, Sei YJ, Park H, Kim J, Ryu Y, Choi JJ, et al. Microengineered human blood-brain barrier platform for understanding nanoparticle transport mechanisms. Nat Commun. 2020;11(1):175. Available from: doi:10.1038/s41467-019-13896-7.
8. Shin W, Hinojosa CD, Ingber DE, Kim HJ. Human intestinal morphogenesis controlled by transepithelial morphogen gradient and flow-dependent physical cues in a microengineered gut-on-a-chip. iScience. 2019;15:391-406. Available from: doi:10.1016/j.isci.2019.04.037.
9. Shao J, Wu L, Wu J, Zheng Y, Zhao H, Jin, Q et al. Integrated microfluidic chip for endothelial cells culture and analysis exposed to a pulsatile and oscillatory shear stress. Lab Chip. 2009;9(21):3118-25. Available from: doi:10.1039/b909312e.
10. Grosberg A, Nesmith AP, Goss JA, Brigham MD, McCain ML, Parker KK. Muscle on a chip: In vitro contractility assays for smooth and striated muscle. J Pharmacol Toxicol Methods. 2012;65(3):126–35. Available from: doi:10.1016/j.vascn.2012.04.001.
11. Zhang YS, Arneri A, Bersini S, Shin SR, Zhu K, Goli-Malekabadi Z, et al. Bioprinting 3D microfibrous scaffolds for engineering endothelialized myocardium and heart-on-a-chip. Biomaterials. 2016;110:45–9. Available from: doi:10.1016/j.biomaterials.2016.09.003.
12. Chen X, Zhang YS, Zhang X, Liu C. Organ-on-a-chip platforms for accelerating the evaluation of nanomedicine. Bioact Mater. 2020;6(4):1012–27. Available from: doi:10.1016/j.bioactmat.2020.09.022.
13. Zhang D, Shadrin I, Lam J, Xian HQ, Snodgrass R, Bursac N. Tissue-engineered cardiac patch for advanced functional maturation of human ESC-derived cardiomyocytes. Biomaterials. 2013;34(23):5813–20. Available from: doi:10.1016/j.biomaterials.2013.04.026.
14. Zhang X, Wang T, Wang P, Hu N. High-throughput assessment of drug cardiac safety using a high-current impedance detection technology-based heart-on-a-chip system. Micromachines. 2016;7(7):122. Available from: doi:10.3390/mi7070122.
15. Candarlioglu PL, Negro GD, Hughes D, Balkwill F, Harris K, Green H, et al. Organ-on-a-chip: Current gaps and future directions. Biochem Soc Trans. 2022;50(2):665–73. Available from: doi:10.1042/BST20200561.
16. Tzatzalos E, Abilez OJ, Shukla P, Wu JC. Engineered heart tissues and induced pluripotent stem cells: Macro- and microstructures for disease modeling, drug screening, and translational studies. Adv Drug Deliv Rev. 2016;96:234–44. Available from: doi:10.1016/j.addr.2015.09.010.
17. Naehrig S, Chao CM, Naehrlich L. Cystic fibrosis. Dtsch Arztebl Int. 2017;114(33–4):564–74. Available from: doi:10.3238/arztebl.2017.0564.
18. Standen J. Cystic fibrosis. InnovAiT. 2020;13(1):39–46. Available from: doi:10.1177/1755738019883322.
19. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: A global perspective. Lancet Respir Med. 2020;8(1):65–124. Available from: doi:10.1016/S2213-2600(19)30337-6.
20. Ramalho AS, Amato F, Gentzsch M. Patient-derived cell models for personalized medicine approaches in cystic fibrosis. J Cyst Fibros. 2023;22(1):S32–8. Available from: doi:10.1016/j.jcf.2022.11.007.
21. Silva IAL, Laselva O, Lopes-Pacheco M. Advances in preclinical in vitro models for the translation of precision medicine for cystic fibrosis. J Pers Med. 2022;12(8):1321. Available from: doi:10.3390/jpm12081321.
22. McCarron A, Donnelley M, Parsons D. Airway disease phenotypes in animal models of cystic fibrosis. Respir Res. 2018;19(1):54. Available from: doi:10.1186/s12931-018-0750-y.
23. Plebani R, Potla R, Soong M, Bai H, Izadifar Z, Jiang A, et al. Modeling pulmonary cystic fibrosis in a human lung airway-on-a-chip. J Cyst Fibros. 2022;21(4):606–15. Available from: doi:10.1016/j.jcf.2021.10.004.
24. Tabary O, Zahm JM, Hinnrasky J, Couetil JP, Cornillet P, Guenounou M, et al. Selective up-regulation of chemokine IL-8 expression in cystic fibrosis bronchial gland cells in vivo and in vitro. Am J Pathol. 1998;153(3):921–30. Available from: doi:10.1016/S0002-9440(10)65633-7.
25. Human organs-on-chips [Internet]. Wyss Institute. 2014. Available from: https://wyss.harvard.edu/technology/human-organs-on-chips/ [cited 2023 Feb 21].
26. Danku AE, Dulf EH, Braicu C, Jurj A, Berindan-Neagoe I. Organ-on-a-chip: A survey of technical results and problems. Front Bioeng Biotechnol. 2022;10:840674. Available from: doi:10.3389/fbioe.2022.840674.
27. Koyilot MC, Natarajan P, Hunt CR, Sivarajkumar S, Roy R, Joglekar S, et al. Breakthroughs and applications of organ-on-a-chip technology. Cells. 2022;11(11):1828. Available from: doi:10.3390/cells1111828.

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